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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,694	01/27/2004	Sherwin V. Kevy	1459.008A	1436

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EXAMINER	
SCHUBERG, LAURA J	

ART UNIT	PAPER NUMBER
1657	

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09/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.**	**Applicant(s)**	
	10/765,694	KEVY ET AL.	
	Examiner	**Art Unit**	
	LAURA SCHUBERG	1657	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 August 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-18,21 and 22*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Continuation of 11. does NOT place the application in condition for allowance because: While Applicant's amendments have overcoming the rejection under 35 USC 112 second paragraph, the claims remain rejected under 35 USC 103(a).

Applicant argues that the Gray patent does not teach the cryoprecipitation of whole blood without a plasma isolation step.
This is not found persuasive because Gray et al explicitly teach the cryoprecipitation of whole blood OR blood plasma which has been anticoagulated (column 4 lines 39-49).

Applicant argues that one of skill in the art would recognize that cryoprecipitation is only ever performed on plasma and there is no apparent reason that one can glean from Gray for substituting a chemical method of precipitation for cryoprecipitation, particularly where the starting material is whole blood.
This is not found persuasive because clearly the Gray patent teaches cryoprecipitation on whole blood (column 4 lines 39-49) and Cochrum clearly teaches that both cryoprecipitation and ethanol precipitation are suitable for the sequestering of an adhesive agent such as prothrombin and thrombin (column 2 lines 15-25).

Applicant argues that the teachings of Cochrum relate to the preparation of purified fibrinogen and are therefore completely inapposite to Applicant's method as currently claimed which seeks to produce thrombin that is virtually free of fibrinogen. Applicant asserts that one cannot extrapolate a method for one protein to another unrelated protein. Applicant asserts that one of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Cochrum and Gray to achieve Applicant's invention as currently claimed.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).
The disclosure of Cochrum et al is drawn to the making of hemostatic agents from human blood which puts it in the same field of endeavor as Gray et al which is also drawn to the making of hemostatic agents from blood. Cochrum et al specifically states that the production of a blood fraction used as an adhesive agent may be obtained by cryo-precipitation or by precipitation with ethanol, centrifugation or ammonium sulfate. Clearly the precipitation of fibrinogen, which leaves behind the prothrombin fraction in the supernatant, is known to be achieved by several different suitable precipitation methods in the prior art. Clearly Cochrum et al suggest that these precipitation methods are equivalents in the art of obtaining hemostatic agents from a patient's own blood and that any one of them would be considered acceptable alternatives (column 2 lines 15-25). In addition Coelho et al demonstrate that ethanol can be used to precipitate either a plasma fraction or whole blood to produce a hemostatic agent thus suggesting that if the precipitating agent works for one sample type it will work for the other as well.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case the obviousness rejections are based on what was taught by the prior art and therefore the rejections are proper.

Applicant argues that the Coelho et al embodiment utilizing whole blood as the starting material is not enabled by the disclosure of Coelho et al. Applicant asserts that specification of Coelho et al contains no guidance from which one skilled in the art, using knowledge of whole blood and its fractionation, would conclude that whole blood and plasma are interchangeable in the Coelho et al method. Applicant asserts that the submitted evidence (including the 132 declaration, the article by ThermoGenesis, and the brochure for the device used by Coelho et al) prove that the Coelho et al method was not enabled with regard to using whole blood.
This is not found persuasive because the claimed invention of Coelho et al has in fact been patented (US 6,472,162), and thus the Office has determined that the method of Coelho et al is in fact enabled with respect to whole blood. In addition the fractionation of whole blood by precipitating proteins is known in the prior art as demonstrated by the teachings of Xiao et al and Gray et al (both cited in previous and current rejections) as well as by Demopoulos et al (page 305, column 2, lines 13-17), Weissbach et al (page 808, 2nd paragraph) and Meucci et al (US 5,135,875 column 6 lines 29-32). Clearly the fractionation of whole blood by precipitation is an alternative known in the prior art and thus the Coelho et al embodiment utilizing whole blood does not require additional teachings beyond what is provided in the specification of Coelho et al and the prior art to be considered enabled. While Applicant's claimed method may not be the standard method in the art, the prior art references cited in the 35 USC 103 rejections above clearly demonstrate that the claimed method is not nonobvious.

Applicant argues that nowhere do any of the claims of the Coelho patent recite mixing whole blood with ethanol. Applicant asserts that the claims fail to teach or suggest the mixing of ethanol with whole blood.
This is not found persuasive because the method claims of a patent are required to include all essential method steps and therefore since the claims of Coelho do not include isolating plasma from whole blood the claims must therefore require that the prothrombin is sequestered from whole blood as the claims explicitly state (see claim 55 column 14 and claim 97 column 16 for examples). The claims state "sequestering prothrombin from whole blood by addition of ethanol". There is no method step included in these claims for the isolation of plasma or the sequestering of prothrombin from plasma and therefore this step is NOT present in these claims.

Applicant argues that the Declaration filed under 37 CFR 1.132 of Sherwin V. Kevy,M.D. 06/04/2007 demonstrated that no report of a method of producing thrombin using whole blood without plasma isolation step had been made.
The declaration under 37 CFR 1.132 filed 06/14/2007 is insufficient to overcome the rejection of claims 1-18 and 21 based upon the references cited under USC 103 as set forth in the last Office action because: It include(s) statements which amount to an affirmation that the affiant has never seen the claimed subject matter before. This is not relevant to the issue of nonobviousness of the claimed subject matter and provides no objective evidence thereof. See MPEP § 716. The references cited in the USC 103 rejections (especially Coelho) clearly demonstrate that the producing of thrombin from whole blood was known, suggested and considered in the prior art.

Applicant argues that Rock et al and Sato et al do not relate to the precipitation of either whole blood or plasma for the recovery of a

coagulant material like thrombin. Applicant asserts that these references do not compensate for the deficiencies in the teachings of Coelho et al.

This is not found persuasive because the teaching of Rock et al was cited in the obviousness rejection to demonstrate that the anticoagulants claimed by Applicant are well known in the art and that their presence in the method of Coelho et al would have been obvious if not inherent. The reference of Sato et al was cited in the obviousness rejection to demonstrate that the advantages of adding mannitol to blood were well known in the art and that their addition to the method of Coelho et al would have been obvious due to these well known advantages. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the previous Office Action has provided no reasoning or explanation for the contention that the purification and optimization of the thrombin product would have been obvious.

This is not found persuasive because the previous Office Action did in fact provide reasoning AND explanation at page 17 first paragraph wherein "the purification and optimization of the final product of thrombin to remove or reduce inhibiting proteins would have been an obvious modification as well". The addition of purification steps to a method of isolating a product provides a product that is more pure and without byproducts to hamper the activity of the product. If Applicant is contending that it is unknown and nonobvious to purify products then evidence supporting this conclusion would have to be submitted for consideration.

Applicant argues that inherency has no place in the determination of obviousness under 35 USC Section 103.

This is not found persuasive because the express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." In re Napier, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). (MPEP 2112 [R3]). From the few method steps that are included in Applicant's claimed method it would appear that the product as claimed is produced by these method steps without a special purification step. Yet Applicant keeps insisting that the use of whole blood produces associated proteins and cells that would produce a thrombin product that would be undesirable because of its lack of purity. It is unclear if Applicant's claimed method steps produce the product with its claimed characteristics or if purification steps are needed for this final result. If purification steps are needed for this final purified product then it would appear that Applicant's claimed method is missing these essential method steps. In any event, the obviousness rejections are based on the teachings of the prior art that the claimed method steps are known and that the since the prior art is silent with regard to the purity of the final product that either the final product is the same assuming that carrying out the obvious method steps would produce this product or that one of ordinary skill in the art would be motivated with a reasonable expectation of success to apply any purification step that would produce a purified superior thrombin product in the methods of Gray or Coelho.

Applicant argues that Applicant's 1.132 declaration has not been given proper consideration. Applicant asserts that the prior Office Action was largely dismissive in response to Applicant's declaration filed 6/14/2007 which presented evidence of non-obviousness. Applicant asserts that the declaration of Dr Mandle was not given proper consideration with regard to paragraphs 8-10 of the 1.132 declaration filed 01/29/2010.

This is not found persuasive because Applicant's 1.132 declarations have in fact been fully considered and found to be insufficient based on the fact that the arguments presented by Applicant are directed to the unexpected use of whole blood for producing thrombin as being nonobvious and yet this step is explicitly claimed in the Coelho patent. It would not be proper to dismiss the claimed invention of the Coelho patent in favor of Applicant's declaration. Paragraphs 8-10 of the Dr Mandle declaration refer to the Dr Kevy declaration and also state that Dr Mandle was not aware of the process of obtaining thrombin from a whole blood sample prior to Applicant's claimed invention. This statement is also not persuasive for the same reason that the Dr Kevy declaration was found unpersuasive in that the Coelho patent clearly shows that the obtaining of thrombin from whole blood was a known, if less preferred, alternative in the prior art.

Therefore the claims remain rejected under 35 USC 103(a) as recited in the last Office Action..